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Co-relation of Lipid Profile with Proteinuria in Sickle Cell Nephropathy Patients for Local Area of Chhattisgarh

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ABSTRACT

Pulmonary hypertension (PH) in sickle cell disease (SCD) is an emerging and important clinical problem. In a single-institution adult cohort of 75 patients, we investigated lipid and lipoprotein levels and their relationship to markers of intravascular hemolysis, vascular dysfunction and PH. In agreement with prior studies, we confirm significantly decreased plasma levels of total cholesterol, high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) in SCD vs. ethnically-matched healthy controls. Several cholesterol parameters correlate significantly with markers of anemia, but not endothelial activation or PH. More importantly, serum triglyceride levels are significantly elevated in SCD compared to controls. Elevated triglyceride levels correlate significantly with markers of hemolysis (lactate dehydrogenase and arginase; both $p<0.0005$), endothelial activation (soluble E-selectin, $p<0.0001$; soluble P-selectin, $p=0.02$; soluble vascular cell adhesion molecule-1, $p=0.01$), inflammation (leukocyte count, $p=0.0004$; erythrocyte sedimentation rate, $p=0.02$) and PH (amino-terminal brain natriuretic peptide, $p=0.002$; prevalence of elevated tricuspid regurgitant velocity (TRV), $p<0.001$). In a multivariate analysis, triglyceride levels correlate independently with elevated TRV ($p=0.002$). Finally, forearm blood flow studies in adult patients with SCD demonstrate a significant association between increased triglyceride/HDL-C ratio and endothelial dysfunction ($p<0.05$). These results characterize elevated plasma triglyceride levels as a potential risk factor for PH in SCD.

KEYWORDS: *Pulmonary hypertension (PH), sickle cell disease (SCD), low-density lipoprotein-cholesterol (LDL-C) , high-density lipoprotein-cholesterol (HDL-C)*

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INTRODUCTION

Sickle cell disease (SCD) is a hemoglobinopathy characterized by red cell rigidity, compromised perfusion and tissue infarction. Chronic hemolysis, another pathological feature of SCD drawing increased attention, gives rise to diminished bioavailability of nitric oxide (NO), oxidant stress and endothelial activation(Aslan, *et al* 2001, Kato, *et al* 2006, Kaul, *et al* 2000, Nath, *et al* 2000, Reiter, *et al* 2002). It is now appreciated that certain complications of SCD may derive from progressive hemolysis-associated vasculopathy, including pulmonary hypertension (PH), cutaneous leg ulceration, priapism, and possibly stroke (Kato, *et al* 2007).

In recent years, PH, a proliferative vascular disease of the lung, has been recognized as a major complication and independent correlate with death among adults with SCD. Pulmonary artery (PA) systolic pressure (PASP) can be estimated by Doppler echocardiography, utilizing the tricuspid regurgitant velocity (TRV). A TRV of 2.5–2.9 m/s is at least two standard deviations above the mean and is considered representative of borderline or mildly elevated PASP, whereas a TRV 3.0 m/s of higher, approximately three standard deviations above the mean, represents significantly elevated PASP, often meeting criteria for pulmonary arterial hypertension. Increased TRV is estimated to be present in approximately one-third of adults with SCD and is associated with early mortality (Ataga, *et al* 2006, Gladwin, *et al* 2004).

In the more severe cases, increased TRV is associated with histopathologic changes such as plexogenic changes and hyperplasia of the pulmonary arterial intima and media (Adedeji, *et al* 2001, Graham, *et al* 2007, Haque, *et al* 2002, Manci, *et al* 2003). These histopathological changes are very similar to those seen in the arterial wall thickening of atherosclerosis. Indeed, PH and atherosclerosis share several overlapping pathophysiologic features, including vascular smooth muscle proliferation, decreased NO bioavailability, oxidant stress, endothelial dysfunction, endothelial activation, increased levels of endogenous NOS inhibitors, platelet activation, in situ thrombosis, and accelerated renal insufficiency(Kato and Gladwin 2008).

Atherosclerosis is characterized by increased accumulation of cholesterol in arterial wall macrophages and is exacerbated by oxidant stress. PH in SCD is also characterized by oxidant stress caused by intravascular hemolysis, but atheromas are not typically present in SCD patients. This might be due to low levels of plasma total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in SCD patients (Buchowski, *et al* 2007, el-Hazmi, *et al* 1987, el-Hazmi, *et al* 1995, Marzouki and Khoja 2003, Sasaki, *et al* 1983, Shores, *et al* 2003, Stone, *et al* 1990, Westerman 1975). Thus, the vasculopathy of PH in SCD does not seem attributable to increased TC or LDL-C levels. Intriguingly, however, there have been scattered

positive reports of low HDL-C(Sasaki, *et al* 1983, Stone, *et al* 1990) and increased triglyceride(Buchowski, *et al* 2007, Kato, *et al* 2005, Morris, *et al* 2005)in SCD patients – features widely recognized in the general population as important contributory factors in cardiovascular disease. Investigation of potential roles for low HDL and high triglyceride levels in the development of PH in SCD therefore is of interest.

Our group has recently shown that besides decreased NO bioavailability, factors associated with PH in SCD include altered apolipoprotein levels and other features shared with atherosclerosis (Hebbel, *et al* 2004, Kato and Gladwin 2008, Morris, *et al* 2005, Yuditskaya, *et al* 2009). Proteomics analysis in a small cohort of 56 patients with and without pulmonary hypertension identified lower apoA-I and suggested higher apoA-II and serum amyloid A levels in SCD patients with PH (Yuditskaya, *et al* 2009). Furthermore, in a physiological test of endothelial function, patients with lower apoA-I had a blunted vasodilatory response to infusion of the endothelium-dependent vasodilator acetylcholine (Yuditskaya, *et al* 2009). Patients with SCD have 3-fold higher levels than healthy controls of the endogenous NO synthase inhibitor asymmetric dimethylarginine, particularly in those patients with elevated TRV (Kato, *et al* 2009, Landburg, *et al* 2008). Additionally, triglyceride levels have also been suggested to be elevated in patients with increased endothelial activation(Kato, *et al* 2005) and increased plasma arginase levels(Morris, *et al* 2005), which in turn were linked to increased pulmonary pressures.

These findings and the therapeutic potential to modulate serum lipids with several commonly used drugs prompted us to investigate in greater detail the serum lipid profile in patients with SCD and possible relationship to vasculopathic complications such as PH. In this study, we present our findings on the status of lipid and lipoprotein levels in a large adult sickle cell cohort at the National Institutes of Health. We confirm decreased serum levels of total cholesterol, LDL-C and HDL-C and increased serum levels of triglycerides in SCD patients, compared to ethnically-matched healthy controls. Decreased total cholesterol, LDL-C and HDL-C were significantly associated with severity of anemia, whereas increased triglyceride levels were associated with hemolysis, vascular dysfunction, and increased prevalence of pulmonary hypertension.

Materials & Methods: Total75 patients were admitted. All patients were subjected to routine blood investigations, blood glucose, urine analysis, routine biochemical investigations, sickling, lipid profile, ECG, Serum Protein, X Ray chest, USG(KUB), serum calcium, potassium, chloride, sodium, phosphorus, albumin, globulin, bilirubin triglyceride, HDL, LDL, VLDL, SGOT, SGPT, Hb Electrophoresis, Serum Thyroid levels.

Result:

- Mean age of the patients was 26.8 ± 11.6 years.
- Males were 29.41% & Females were 70.59%, Ratio being M: F: 1:2.75.
- In patients of Sickle cell nephropathy, 41.4% patients had deranged lipid profile.
- In Sickle cell trait, 27.2 % had deranged lipid profile.
- Among Sickle cell disease, all the patients had deranged lipid profile.
- Derangement in individual lipids are as follows:-

1. Hypercholesterolemia(≥ 200 mg/dl) - 7.31 %,
2. TG(≥160 mg/dl) - 7.31%,
3. LDL (Ëƒ130 mg/dl) – 2.4%
4. HDL (≤40 mg/dl) - 58.5% .

- Proteinuria in patients of Sickle cell nephropathy:

<1 gm/d = 21.9% had deranged lipid profile.
>1 gm/d = 34.1 % patients had deranged lipid profile.

Conclusion:

1. Lipid derangement is almost seen in all the patients of Sickle cell Nephropathy.
2. Hypercholesterolemia & Hypertriglyceridemia is common in males then in female.
3. Low levels of HDL was common in females as compare to male.
4. Deranged lipid profile was more common in proteinuria more than 1gm/dl

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